REMARKS

The Present Invention

The present invention is directed to an MHC-I antigen-negative and MHC-II antigen-negative universal bystander human cell line, which has been modified by introduction of a nucleic acid molecule comprising a nucleic acid sequence encoding GM-CSF operably linked to a promoter. The universal bystander cell line expresses about 500 ng or greater GM-CSF/10^6 cells/24 hours. The present invention is also directed to a composition comprising the universal bystander cell line and a cancer antigen, a method of making the universal bystander cell line, a method of stimulating an immune response to a cancer in a human patient by administering to the patient the composition, which has been irradiated, and a method of cancer immunotherapy, in which the improvement comprises administering to a human patient having cancer the irradiated composition.

The Pending Claims

Claims 1-14, 17-28, 40-47 and 50-53 are currently pending. Claims 1-14 are directed to the universal bystander cell line, whereas claims 17-21 are directed to the composition comprising the universal bystander cell line and a cancer antigen, claims 22-28 are directed to the method of making the universal bystander cell line, claims 40-47 are directed to the method of stimulating an immune response, and claims 50-53 are directed to the improved method of cancer immunotherapy.

Amendments to the Claims

Claim 2 has been amended to address matters of form. No new matter has been added by way of these amendments.

The Final Office Action

The Office has maintained the rejections of all of the pending claims under 35 U.S.C. § 112, first paragraph, for alleged lack of description and alleged lack of enablement, and under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Office also has maintained the rejection of claims 1, 5, 7, 17, 20, 22, 28, 40, 41, 44, 45, 50 and 52 under 35 U.S.C. § 103(a) as obvious in view of and, therefore, unpatentable over Dranoff et al. in view of Ferrone et al., as allegedly evidenced by Thomas et al., alone or in further view of Shepard

et al. or Polack et al. Claims 1-14, 17-28, 40-47 and 50-53 remain rejected under the juidically created doctrine of obviousness-type double-patenting as unpatentable over claims 1-21 of U.S. Pat. No. 6,464,973. Reconsideration of these rejections is hereby requested.

Discussion of Rejections under 35 U.S.C. § 112, first paragraph

All of the pending claims stand rejected under Section 112, first paragraph, for allegedly lacking description and enablement. This rejection is traversed for the reasons set forth below.

The Office clearly understands that Applicants' use of the term "naturally" to describe the lack of MHC-I and MHC-II antigens on the universal bystander cell line encompasses a cell line that lacks MHC-I and MHC-II antigens due to a naturally occurring mutation, such as a cancerous mutation. However, the Office contends that use of the term "naturally" to encompass such a cell line is contrary to the ordinary meaning of the term, citing *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 U.S.P.Q.2d 1029, 1033 (Fed. Cir. 1999).

At issue in *Process Control* was whether a term, recited in two different clauses of a single claim, should be construed to have the same meaning in both clauses. The Federal Circuit found that the claim language was "susceptible to only one meaning," based on "the language of the claim itself." Id. at 1356. According to the Federal Circuit, the claim language was not susceptible to two different constructions. Id. The Federal Circuit further found that the written description did not clearly redefine the disputed claim term so as to put a reasonable competitor or one skilled in the art on notice that the patentee intended to give the claim term a meaning contrary to its ordinary meaning. Id. at 1357.

Like *Process Control*, the present specification does not redefine the term "naturally" contrary to its ordinary meaning. The specification makes it clear that "naturally" is distinguished from "modified." See, for example, the specification at page 5, lines 3-6, where the universal bystander cell line is described as a human cell line, which either "naturally lacks" MHC-I antigens and MHC-II antigens, or is "modified" so that it lacks MHC-I antigens and MHC-II antigens. What is meant by "modified" is evidenced in the specification at, for example, page 7, lines 12-14, wherein it is stated that cells that lack MHC-I antigens can be achieved by interfering with the expression and/or transport of the α

chain, whereas cells that lack MHC-II antigens can be achieved by interfering with the expression and/or transport of the α and β chains. Thus, a cell line that has been modified so that it lacks MHC-I and MHC-II antigens is one that lacks MHC-I and MHC-II antigens due to manipulation by man. In contrast, a cell line that naturally lacks MHC-I and MHC-II antigens is one that lacks MHC-I and MHC-II antigens without manipulation by man, i.e., it never had MHC-I and MHC-II antigens or, as a result of the effects of nature, it came to lack MHC-I and MHC-II antigens. This is supported by the Office's reference to a standard English dictionary as evidencing that the term "naturally" means "by nature, inherently," "without a doubt," and "present or produced by nature" (see Office Action dated April 10, 2003, at page 3, third full paragraph) and the Office's acknowledgement that "naturally" encompasses cells, which have lost the capacity to express MHC antigens as a result of naturally occurring mutations, as supported by the references previously provided by Applicants (see Office Action dated April 10, 2003, at page 4, first full paragraph).

Furthermore, like *Process Control*, the use of the term "naturally" in the claims is not susceptible to more than one meaning. For the Office to characterize the loss of MHC antigen expression due to a cancerous mutation as not "naturally" occurring (see the top of page 5 of the Office Action dated April 10, 2003) is directly contrary to the evidence of record, including the evidence entered into the record by the Office, itself, by way of the Office Action dated April 10, 2003. This is tantamount to saying that mutations, including cancerous mutations, do not occur naturally, and that every person, who has cancer, has cancer because his/her body was modified, or manipulated by man, in some way to cause the cancer. Applicants maintain that this is the only and, hence, ill-founded basis upon which the Office can continue to maintain a rejection for lack of written description.

The Office goes on to contend that the specification fails to disclose a universal bystander cell line that naturally lacks MHC-I and MHC-II antigens. The Office opines that the only cell known to lack naturally MHC-I and MHC-II antigens is a red blood cell, for which there is no known cell line, and that mutated tumor cell lines, to the extent that they are encompassed by use of the term "naturally," vary widely in cell-surface markers. Based on this premise, the Office contends that one can not predictably determine which cell line meets the limitations of the claims.

Applicants respectfully disagree. Applicants teach the K562 cell line, which lacks MHC-I and MHC-II antigens. In addition, Applicants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigens by searching the PubMed database. Applicants have previously pointed out that numerous examples of such cell lines were known in the art prior to February 2, 1998, the date to which the instant application claims priority, including Wang et al. (1993), Ferrone et al., Kageshita et al., and Wang et al. (1996) (see Response to Office Action dated April 10, 2003, at page 5, for example).

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003), the Federal Circuit clarified its position in *Regents of the Univ. of Calif. v. Eli Lilly &Co.*, 119 F.3d 1559 (Fed. Cir. 1997), regarding functional descriptions of genetic material. In *Amgen*, the Federal Circuit stated that "*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." Id. at 1332. The Federal Circuit went on to say that the facts of both *Eli Lilly* and *Enzo Biochem v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002), do not comport with the facts of *Amgen* because "the claim terms at issue here [referring to *Amgen*] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." *Amgen*, 314 F.3d at 1313.

In view of the above, the claim terms directed to cell lines that lack MHC-I and MHC-II, being known in the art, convey sufficient "information concerning [their] identity such that one of ordinary skill in the art could visualize or recognize the identity of the members of the genus." *Id. quoting Eli Lilly*, 119 F.3d at 1567, 1568. Thus, whether or not there is a red blood cell line is of no import. Likewise, the fact that tumor cell lines may vary widely in cell-surface markers also is of no import.

As previously argued, whether or not a given human cell line naturally lacks MHC-I and MHC-II antigens is readily ascertainable -- either the human cell line expresses MHC-I and/or MHC-II or it does not. In this regard, the instant specification teaches antibodies (see, e.g., Example 1), which can be used to determine MHC antigen expression, or lack thereof, also as taught by the instant specification (see, e.g., Example 1). Therefore, there is no basis for the Office to contend that one of ordinary skill in the art cannot determine whether a cell line lacks MHC-I and MHC-II antigens. Furthermore, database searching for such cell lines

and routine screening of cell lines, even if on a "large-scale" basis, do not constitute undue experimentation. See, e.g., *In re Wands*, 858 F.2d 731, 736-737 (Fed. Cir. 1988). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.* at 737. The fact that the Office found 471 hits upon searching "HLA loss and tumors" does not evidence undue experimentation. In view of the foregoing and in view of the fact that Applicants need not describe that which is known in the art, Applicants submit that the subject matter of the claims is adequately described.

Therefore, statements made by the Office, such as "naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material," and "claiming all cell lines having a common trait without defining what means will do is not in compliance with the description requirement," citing *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993), and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CAFC 1997), clearly do not apply to the instant claims. Likewise, the citation to *Amgen Inc. v. Chugai Pharma. Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), for the proposition that "conception of chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological activity,"also does not apply to the instant claims. As discussed above, *Eli Lilly* does not apply to the present case because cell lines lacking MHC-I and MHC-II are known in the art. Similarly, the arguments made above in connection with *Amgen v. Hoechst* apply to *Fiers* and *Amgen v. Chugai*. Since cell lines lacking MHC-I and MHC-II are known in the art, those ordinarily skilled in the art are able recognize the identity of the members of the genus. Accordingly, the claims are not overly broad, and are not indefinite under 35 U.S.C. § 112, first paragraph.

In the event that the Office is not persuaded by the above arguments, Applicants would be amenable to amending claim 1 as follows:

1. (Currently amended) A major histocompatibility class I (MHC-I) antigen-negative and major histocompatibility class II (MHC-II) antigen-negative universal bystander human cell line, which ~~:~~

~~(i) is a human cell line,~~

~~(ii) naturally lacks major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens, and~~

~~(iii) is~~ has been modified by introduction of a nucleic acid molecule comprising a nucleic acid sequence encoding granulocyte macrophage-colony stimulating factor (GM-CSF) operably linked to a promoter,

wherein said universal bystander cell line expresses about 500 ng or greater GM-CSF/10^6 cells/24 hours.

With regard to enablement, the Office contends that the specification fails to disclose another species of a cell line lacking MHC-I and MHC-II antigens in addition to the K562 cell line and that, therefore, undue experimentation is required to search for other examples of cell lines, citing *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361 (CAFC 1997). At issue in *Genentech* was whether the specification described how to make hGH using cleavable fusion expression. The court found that undue experimentation was required because the specification did not describe any specific starting material or any of the reaction conditions for the steps needed to produce hGH. Id. at 1365-66. Unlike the specification at issue in *Genentech*, the present specification teaches antibodies that can be utilized to establish the presence or absence of MHC antigen expression. "[T]he enablement requirement is met if the description enables any mode of making and using the invention." *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991). Furthermore, "representative samples are not required by the statute and are not an end in themselves." *Amgen, Inc., v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 quoting In re Robins, 429 F.2d 452, 456-7 (CCPA 1970). Accordingly, since the specification provides a mode of practicing the invention, another species of a cell line lacking MHC-I and MHC-II antigens in addition to the K562 cell line is not required.

In this regard, the Office again contends that the art reports that the SK-MEL-33 cell line and the cell lines of Ferrone et al. and Wang et al. do not lack both MHC-I and MHC-II. (NOTE: The Office's characterization of Ferrone et al. contradicts its characterization of Ferrone et al. with respect to the obviousness rejections.) As Applicants have previously pointed out, this can be explained by differences in subclones. Also, as previously pointed

out, this does not detract from the other examples of cell lines, which lack MHC-I and MHC-II expression, provided by Applicants.

On another note, the Office contends that the claims encompass and the specification exemplifies melanoma cells, which the art reportedly teaches require the presence of animal serum, while the claims are directed to the use of defined medium, which the specification defines as serum-free at page 14, line 26. Applicants point out that defined medium is only recited in dependent claims (see, e.g., claims 6, 9, 26 and 27). Furthermore, as taught in the instant specification at, for example, page 5, lines 18-19, the ability of the universal bystander to grow in defined, i.e., serum-free, medium is preferred -- not required. In response to the Office's contention regarding melanoma cells, Applicants point out that melanoma cells can be "weaned" of their requirement for animal serum by gradually reducing the amount of serum in the growth medium. For example, it is a matter of routine to gradually reduce the amount of serum in cell growth medium from 10% to 5% to 2.5%, until serum is not longer required.

Discussion of Rejections under 35 U.S.C. § 112, second paragraph

All of the pending claims stand rejected under Section 112, second paragraph, as allegedly indefinite. This rejection is traversed for the reasons set forth below.

The Office clearly understands that Applicants' use of the term "naturally" to describe the lack of MHC-I and MHC-II antigens on the universal bystander cell line encompasses a cell line that lacks MHC-I and MHC-II antigens due to a naturally occurring mutation, such as a cancerous mutation. However, the Office contends that use of the term "naturally" to encompass such a cell line is contrary to the ordinary meaning of the term, citing *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 U.S.P.Q.2d 1029, 1033 (Fed. Cir. 1999), and arguing that, when a cell mutates, it changes from its natural state.

At issue in *Process Control* was whether a term, recited in two different clauses of a single claim, should be construed to have the same meaning in both clauses. The Federal Circuit found that the claim language was "susceptible to only one meaning," based on "the language of the claim itself." Id. at 1356. According to the Federal Circuit, the claim language was not susceptible to two different constructions. Id. The Federal Circuit further found that the written description did not clearly redefine the disputed claim term so as to put

a reasonable competitor or one skilled in the art on notice that the patentee intended to give the claim term a meaning contrary to its ordinary meaning. Id. at 1357.

Like *Process Control*, the present specification does not redefine the term "naturally" contrary to its ordinary meaning. The specification makes it clear that "naturally" is distinguished from "modified." See, for example, the specification at page 5, lines 3-6, where the universal bystander cell line is described as a human cell line, which either "naturally lacks" MHC-I antigens and MHC-II antigens, or is "modified" so that it lacks MHC-I antigens and MHC-II antigens. What is meant by "modified" is evidenced in the specification at, for example, page 7, lines 12-14, wherein it is stated that cells that lack MHC-I antigens can be achieved by interfering with the expression and/or transport of the α chain, whereas cells that lack MHC-II antigens can be achieved by interfering with the expression and/or transport of the α and β chains. Thus, a cell line that has been modified so that it lacks MHC-I and MHC-II antigens is one that lacks MHC-I and MHC-II antigens without manipulation by man, i.e., it never had MHC-I and MHC-II antigens or, as a result of the effects of nature, it came to lack MHC-I and MHC-II antigens. This is supported by the Office's reference to a standard English dictionary as evidencing that the term "naturally" means "by nature, inherently," "without a doubt," and "present or produced by nature" (see Office Action dated April 10, 2003, at page 3, third full paragraph) and the Office's acknowledgement that "naturally" encompasses cells, which have lost the capacity to express MHC antigens as a result of naturally occurring mutations, as supported by the references previously provided by Applicants (see Office Action dated April 10, 2003, at page 4, first full paragraph).

Furthermore, like *Process Control*, the use of the term "naturally" in the claims is not susceptible to more than one meaning. For the Office to characterize the loss of MHC antigen expression due to a cancerous mutation as not "naturally" occurring (see the top of page 5 of the Office Action dated April 10, 2003) is directly contrary to the evidence of record, including the evidence entered into the record by the Office, itself, by way of the Office Action dated April 10, 2003. This is tantamount to saying that mutations, including cancerous mutations, do not occur naturally, and that every person, who has cancer, has cancer because his/her body was modified, or manipulated by man, in some way to cause the

cancer. Applicants maintain that this is the only and, hence, ill-founded basis upon which the Office can continue to maintain a rejection for alleged indefiniteness.

The rejection of claim 2 as allegedly indefinite with respect to whether or not receptors for EBV are required to be absent is believed to be moot in view of the amendment of the claim. Claim 2 has been amended to recite lowercase Roman numerals to clarify what is required.

In view of the foregoing, Applicants submit that the claims are definite. Accordingly, Applicants request the withdrawal of this rejection.

Discussion of Rejections under 35 U.S.C. § 103(a)

Claims 1, 5, 7, 17, 20, 22, 28, 40, 41, 44, 45, 50 and 52 stand rejected under Section 103 as obvious in view of and, therefore, unpatentable over Dranoff et al., in view of Ferrone et al., as evidenced by Thomas et al. This rejection is traversed for the reasons set forth below.

Dranoff et al. does not teach or suggest a universal bystander cell line as taught by the present invention. Dranoff et al. also does not teach or suggest a composition comprising a universal bystander cell line, a method of making a universal bystander cell line, and a method of stimulating an immune response to a cancer in a human patient by administering the composition comprising a universal bystander cell line. Dranoff et al. does not appreciate the importance of using a cell line that naturally lacks MHC-I and MHC-II as taught by the present invention.

The Office admits that it is unclear whether the B16 melanoma disclosed by Dranoff et al. expresses MHC-I or MHC-II. The Office relies on Ferrone et al. as disclosing that various percentages of primary melanoma, metastatic melanoma, and melanoma cell lines lack MHC-I and normally lack MHC-II. The Office concludes that it would have been obvious to modify the methods of Dranoff et al. by substituting the B16 melanoma with melanoma cells that lack MHC-I and MHC-II as disclosed by Ferrone et al. with a reasonable likelihood of success. While admittedly not relying on Thomas et al., the Office attempts to bolster its reliance on the combined disclosure of Dranoff et al. and Ferrone et al. by pointing to Thomas et al. as disclosing that B78H1, a variant cell line of the B16 melanoma disclosed by Dranoff et al., lacks MHC-I. Thomas et al., however, teaches that the expression, i.e., the

presence, of an allogeneic MHC molecule by a vaccine cell can actually enhance the induction of systemic antitumor immunity (see abstract). Such a disclosure teaches away from the use of a cell line that lacks MHC expression as taught by the present invention.

What the Office clearly fails to appreciate is that there is no teaching or suggestion in Ferrone et al. (alone or in further combination with Thomas et al.) to modify the alleged teachings of Dranoff et al. in the manner proposed by the Office. Therefore, one of ordinary skill in the art would not have been motivated to modify the alleged teachings of Dranoff et al. so as to arrive at the present invention, particularly in view of Thomas et al. In order to establish an obviousness rejection under 103(a), based on a combination of the prior art, the Examiner must show some motivation, suggestion, or teaching to make the specific combination claimed by the Applicant. *In re Kotzab*, 217 F.3d 1365 (Fed. Cir 2000), referring to *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998). Furthermore, the Examiner must "cast the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *Id.* referring to *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

The Examiner fails to point to any motivation or suggestion, either in the prior art or in the then-accepted wisdom in the field, to combine the references. According to the Examiner, "the references are combined to show that one of skilled in the art knows modifying tumor cells with GM-CSF would enhance anti-tumor immunity, and there is motivation to modify different types of tumor cells with GM-CSF, and one line of tumor cells modified may actually lacks both MHC-I and MHC-II." Office Action, pp. 9-10. Yet, the combination of references does not show that one of ordinary skill in the art would have known that modifying tumor cells with GM-CSF would have enhanced anti-tumor immunity for the reason set forth above. "The Examiner can satisfy the burden of showing obviousness of the combination 'only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references.'" *In re Sang-Su Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) *quoting In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). Since the Examiner fails to provide the "objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant

teaching of the references," a *prima facie* case of obviousness cannot be established. In light of the foregoing, Applicants respectfully request withdrawal of this rejection.

Claims 1, 5, 7, 11, 17, 20, 22-24, 28, 40, 41, 44, 45, 50 and 52 stand rejected under Section 103 as obvious in view of and, therefore, unpatentable over Dranoff et al., in view of Ferrone et al., in further view of Shepard et al. or Polack et al. This rejection is traversed for the reasons set forth below.

As indicated above, Dranoff et al. does not teach or suggest a universal bystander cell line as taught by the present invention. Dranoff et al. also does not teach or suggest a composition comprising a universal bystander cell line, a method of making a universal bystander cell line, and a method of stimulating an immune response to a cancer in a human patient by administering the composition comprising a universal bystander cell line. Dranoff et al. does not appreciate the importance of using a cell line that naturally lacks MHC-I and MHC-II as taught by the present invention. Ferrone et al. does not cure the deficiencies of Dranoff et al. for the reasons set forth above. The fact that Shepard et al. or Polack et al. may disclose the use of hygromycin resistance as a selectable marker is of no import then. Neither Shepard et al. nor Polack et al. cures the deficiencies of Dranoff et al. and Ferrone et al.

Therefore, the claimed invention cannot be said to be obvious in view of the cited references. Accordingly, this rejection should be withdrawn.

The Office relies on *In re Keller* and *In re Merck* in support of its contention that Applicants are not addressing the cited references in combination. Applicants, however, adamantly maintain that they have, in fact, argued against the combination of cited references and have argued why the secondary references do not cure the deficiencies of the primary references. In this regard, Applicants point out that their approach differs from the approaches of the cited cases. In *Keller* an affidavit was submitted from an expert that attacked only one reference, not the combination of two references. In the case at hand, Applicants have addressed all of the references. In *Merck* the appellant tried to argue that one of the references taught away from the invention where the rejection was based on a combination of references. Here again, the case at hand is distinguishable from *Merck* inasmuch as Applicants have addressed all of the references.

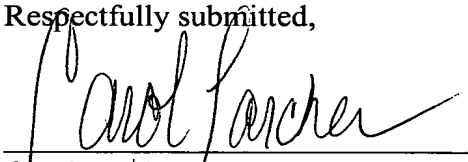
Discussion of Obviousness-Type Double-Patenting Rejection

The Office has rejected claims 1-14, 17-28, 40-47 and 50-53 under the judicially created doctrine of obviousness-type double-patenting as unpatentable over claims 1-21 of U.S. Pat. No. 6,464,973. Upon an indication of allowable subject matter, Applicants will submit a terminal disclaimer, which will render this rejection moot.

Conclusion

In view of the above, the application is considered to be in good and proper form for allowance, and the Office is respectfully requested to pass this application to issuance. If, in the opinion of the Office, a telephone conference would expedite prosecution, the Office is encouraged to contact the undersigned attorney.

Respectfully submitted,



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Date: March 17, 2004

In re Appln. of Levitsky et al.
Application No. 09/992,443

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION (along with the Transmittal Form PTO-1083 (in duplicate) and any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date shown below in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, Express Mail No. EU905097615US.

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Angelica Diaz
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